

Figure 1

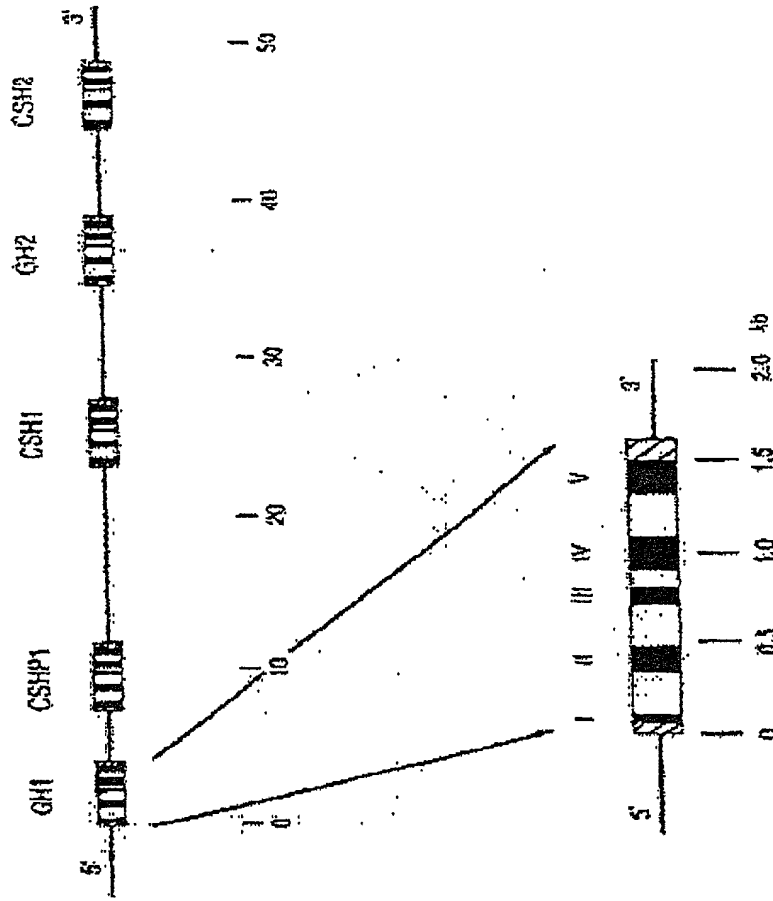


Fig. 1 Human growth hormone gene cluster on chromosome 17q23. The fine structure of the GH1 gene is shown below. The scales are in kilobases (kb)

Figure 2

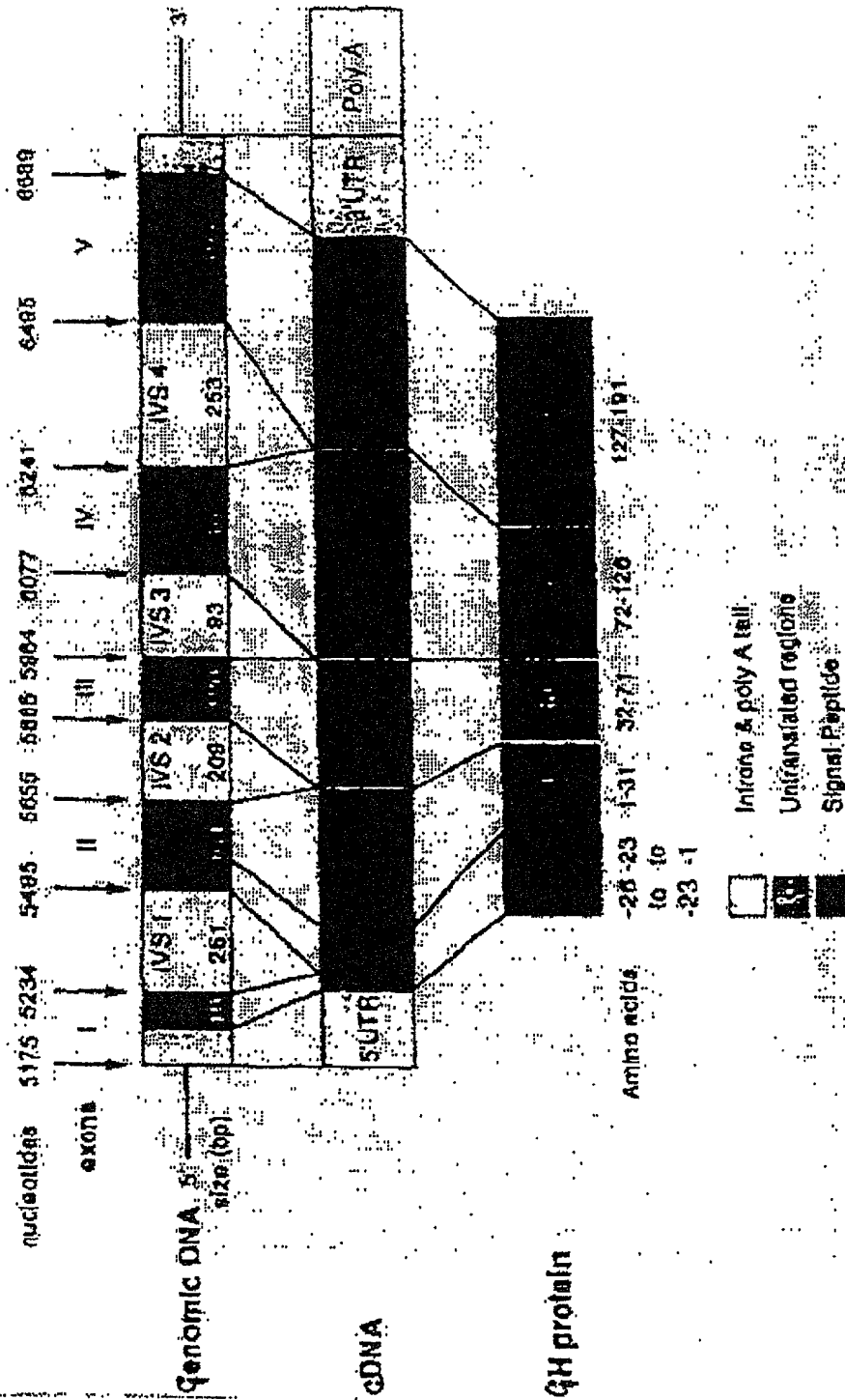


Figure 3

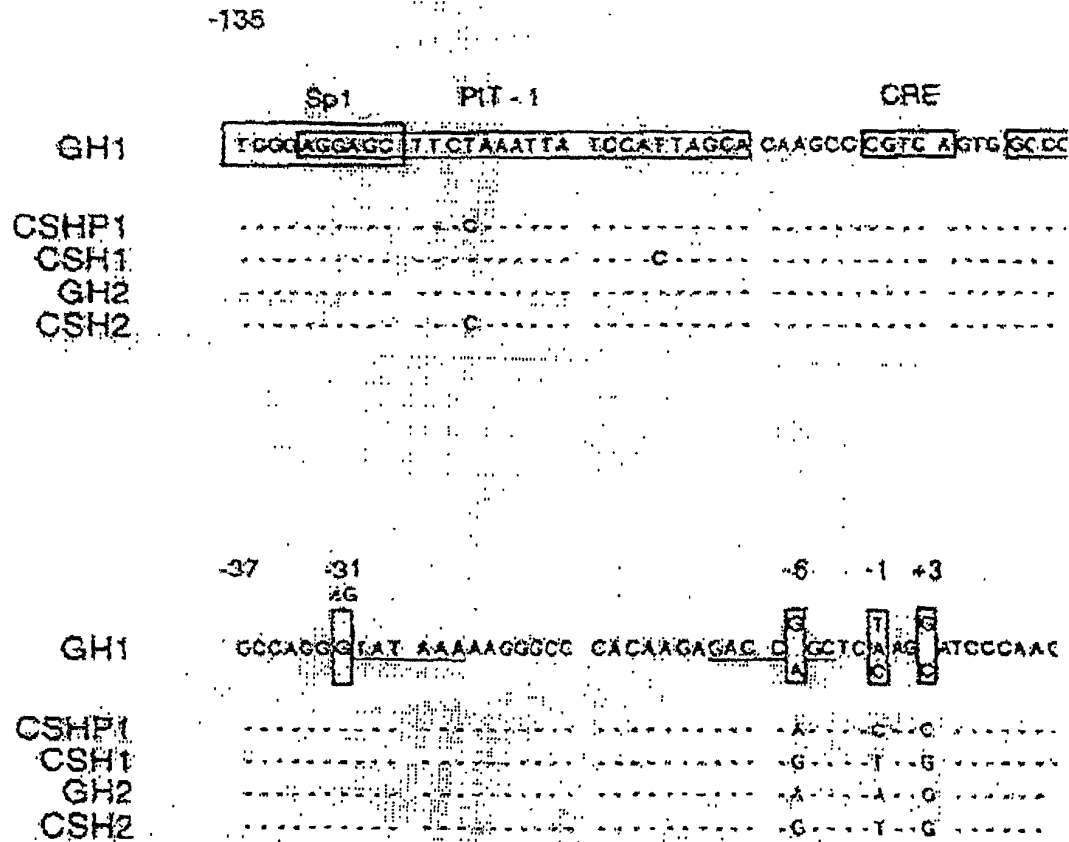


Fig. 3. Structure of the 5' untranslated region and promoter region of the human *GH1* gene. *Horizontal boxes* denote known, putative or inferred binding sites for transcription factors. *Vertical boxes* indicate polymorphic sites in the human population (data from Giordano et al., 1997; Wagner et al., 1997). The numbering scheme is by reference to the transcriptional initiation site at +1. The TATA box, a Chi-like element and the ATG translational initiation site are *underlined*. The human *GH1* promoter is also aligned with the promoters of the human *CSHP1*, *CSH1*, *GH2* and *CSH2* genes in order to indicate both the extent of homology but also the differences evident between promoters.

aaaaaaaaagtgagaagcagctcccactccaggaggaagacacacacatcccgtggacaaggatgcagatgt 751-825
tttttttgcctcgtcgagggtgaggtccctcccttctgtgtgtagggcacctgttctctacgtctaca

5 ggcctttggccttcattcccattcatgcccgggcaggatctgttttcaggaggggaggaagcgcggggcccca 826-900
ccggaaacccgaagtaaggtaagtcggcccgctccctagacaaaagtcctccccgcctccgtcgccccggggt

ccgcctgcagggttatttgcacattttgagccgtgctgttcctcactggtgacaacagccctgagccccattt 901-975
ggcggacgtccaataaacagtgtaaaactcggcacgacaaggagtgaccactgttgtcgggactcggggtaaa

10 tgggctcatgatgcccttttctccagaacaggagggcctcacaaagcctacccctgcctctgcctcggctgccc 976-1050
accgagtactacgggaaaagaagggtcttgcctccggagtgtcggatggggaaggagcgggagccgacggg

ggggcttcacattctgacttctgacgacacctccctttccagggaaggcaacatcaaaaataaggaatgggggccag 1051-1125
ccccgaagtgaagactgaagactgctgtggagggaaggtccttccgtttagttttattccttaccctccggtc

15 ggtcgggcgaagggaacaaagggtcagggggtggggaagcaagaaggcagcagccccagccacctaggatgcc 1126-1200
ccagcccgcttccctgttccccgagtcctccacccctctcgttcttccgtcgctgggggtcgggtgggatcctacgg

20 gggagggggaagaaacctcagggaagaaagagctcagacccctgcctccttctccagcccagggtgtcctggatctg 1201-1275
ccctcccccttcttgagtccttcttcttctcagagtctgggacggaggaagaggtcgggtccacaggaacctagac

ctgggctgctgtgactgggaaaagacctgctaagaaggacgtgggtttgagtcctgacccagcagtgtagcagcc 1276-1350
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25 aggaaacctccccagggttaccagtgggttcttactaagggtggctctgccccaaacggaggagcgtctgcacatg 1351-1425
tcctttggaggggtccaatggtcaccagagatgattcccaccgagacgggggttgctcctccctcgcagacgtgtac

30 catcaggggcaatcgcgctggtctcaatgacccggtgggtgcctggggcggaagggcattggctgggcaagcagag 1426-1500
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5 ttcctgccccacatgccaacagaccccatgaggcaacacccattcttaacctctcagtgaccaagggttcctcat 1501-1575
 aagggaacgggtgtacggtgtcgtgggtactccgttggtggaataaggagagtcactggttccaaggagta
 10 tttcgtaaaatagaaaataagcccaatagcgcgtttttttgtgtgttttctgggggtttttctgagacaagatct 1576-1650
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 15 tgctctgtgtccaggctggagtgagtgagtggtgcaatctccattcacgggcaacctctgccacctggactcaagtga 1651-1725
 acgagacaacaggtccgacctcacgtcaccacgttagaggttaagtgcggttgagagcgtggacctgagttcact
 20 ttcacccacctcagcctccgagtagctgggactacaggtcatgctactacacctggtaaatctgtgtatttctt 1726-1800
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 30 cccaaagtgtgggattacagggcgtgagccactgcgcccggcccccaacagtcggttggaaggcgagctgtgc 1876-1950
 gggtttcacgacctaatgtccgactcggtagcgcgggcggggtgtcacgcaaccagcttcccgtcgacacg
 35 acattgaaggccatcctgcacatctgaggtagcttgggaatgtggtggacggcacgccctgaggaggcgaggagtg 1951-2025
 tgtaacttcggtaggacgtagactcccatgaaccacttacaccacctgccgtgcgggactcctcccgctcctcac
 2026-2030
 cgagg
 gctcc

25 PCR primers are marked in bold (42-1984 = 1942bp).
 Sequencing primers are underlined (GHLCR3.1, 541-558; GHLCR3.2, 1006-1023; GHLCR3.3, 1422-1440;
 GHLCR5.0, 640-658)

Figure 5

	-700	ctgtttcttg	gtttgtgtct	ctgctgcaag	tccaaggagc	tggggcaata	-651
5	-650	ccttgagtct	gggttcttcg	tccccaggga	cctgggggag	ccccagcaat	-601
	-600	gctcagggaa	aggggagagc	aaagtgtggg	gttgggttctc	tctagtggtc	-551
	-550	agtgttggaa	ctgcatccag	ctgactcagg	ctgacccagg	agtcctcagc	-501
	-500	agaagtggaa	ttcaggactg	aatcgtgctc	acaaccccca	caatctattg	-451
	-450	gctgtgcttg	gccccctttc	ccaacacaca	cattctgtct	ggtgggtgga	-401
10	-400	ggttaaaca	gccccggagg	ggaaagggat	aggatagaga	atgggatgtg	-351
	-350	gtcggtaggg	gggtctcaagg	actggctatc	ctgacatcct	tctccgcgtt	-301
	-300	caggttggcc	accatggcct	gccccagag	ggcaccacag	tgacccttaa	-251
	-250	agagaggaca	agttgggtgg	tatctctggc	tgacactctg	tgacaaccc	-201
	-200	tcacaacact	ggtaggggtg	ggaggggaaa	gatgacaagc	cagggggcat	-151
15	-150	gatcccagca	tgtgtgggag	gagcttctaa	attatccatt	agcacaagcc	-101
	-100	cgtcagtggc	cccatgcata	aatgtacaca	gaaacagggtg	ggggcagacag	-51
	-50	tgggagagaa	ggggccaggg	tataaaaagg	gcccacaaaga	gaccagctca	-1
	+1	aggatcccaa	ggcccaactc	ccgaaccac	tcagggtcct	gtggacagct	+50
	+51	cacctagcgg	caATGGCTAC	AGgtaagcgc	ccctaaaatc	cctttgggca	+100
20	+101	caatgtgtcc	tgaggggaga	ggcagcgacc	tgtagatggg	acgggggcac	+150
	+151	taaccctcag	gttttggggct	tctgaatgtg	agtatcgcca	tgtaagccca	+200
	+201	gtatttggcc	aatctcagaa	agctcctggg	ccctggaggg	atggagagag	+250
	+251	aaaaacaac	agctcctgga	gcagggagag	tgctggcctc	ttgctctccg	+300
	+301	gctccctctg	ttgcccctctg	gtttctcccc	agGCTCCCGG	ACGTCCCTGC	+350
25	+351	TCCTGGCTTT	TGGCCTGCTC	TGCTTCCCT	GGCTTCAAGA	GGGCAGTGCC	+400
	+401	TTCCCAACCA	TTCCCTTATC	CAGGCTTTTT	GACAACGCTA	TGCTCCGCGC	+450
	+451	CCATCGTCTG	CACCAGCTGG	CCTTTGACAC	CTACCAGGAG	TTTgtaagct	+500
	+501	cttggggaat	gggtgcgcac	caggggtggc	aggaaggggg	gactttcccc	+550
	+551	cgtgggaaaa	taagaggagg	agactaagga	gctcagggtt	tttcccgaag	+600
30	+601	cgaaaatgca	ggcagatgag	cacacgctga	gtgaggttcc	cagaaaagta	+650
	+651	acaatgggag	ctgggtctcca	gcgtagacct	tggtggggcgg	tccttctcct	+700
	+701	agGAAGAAGC	CTATATCCCA	AAGGAACAGA	AGTATTCAAT	CCTGCAGAAC	+750
	+751	CCCCAGACCT	CCCTCTGTTT	CTCAGAGTCT	ATCCGACAC	CCTCAACAG	+800
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	+951	CAGTCGTGGC	TGGAGCCCCG	GCAGTTCCTC	AGGAGTGTCT	TCGCCAACAG	+1000
	+1001	CCTGGTGTAC	GGCGCCTCTG	ACAGCAACGT	CTATGACCTC	CTAAAGGACC	+1050
	+1051	TAGAGGAAGG	CATCCAAACG	CTGATGGGGg	tgaggggtggc	gccaggggtc	+1100
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	+1201	cttcatttcc	cctcgtgaat	cctccaggcc	tttctctaca	ccctgaaggg	+1250
	+1251	gagggaggaa	aatgaatgaa	tgagaaaggg	agggaaacagt	acccaagcgc	+1300
	+1301	ttggcctctc	cttctcttcc	ttcactttgc	agAGGCTGGA	AGATGGCAGC	+1350
45	+1351	CCCCGACTG	GGCAGATCTT	CAAGCAGACC	TACAGCAAGT	TCGACACAAA	+1400
	+1401	CTCACACAAC	GATGACGCAC	TACTCAAGAA	CTACGGGCTG	CTCTACTGCT	+1450
	+1451	TCAGGAAGGA	CATGGACAAG	GTCGAGACAT	TCCTGCGCAT	CGTGCACTGC	+1500
	+1501	CGCTCTGTGG	AGGGCAGCTG	TGGCTTCTAG	ctgcccgggt	ggcatccctg	+1550
	+1551	tgacccctcc	ccagtgcctc	tcctggccct	ggaagtgtgc	actccagtgc	+1600
50	+1601	ccaccagcct	tgtcct <u>aata</u>	aaattaagtt	gcatcatttt	gtctgactag	+1650
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	+1701	gcaagttagg	aagacaacct	gtagggcctg	cggggtctat	tcgggaacca	+1750
	+1751	agctggagtg	cagtggcaca	atcttggctc	actgcaatct	ccgcctcctg	+1800
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	+2151	tgttgaattc	ctgggcctag	ggctgtgccca	gctgcctcgt	cccgtcacct	+2200
	+2201	tctggcttct	tctctccctc	catatcttag	ctgttttcc	catgagaatg	+2250
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5	+2301	ttatctctgc	cccagtaga	ttgttagctc	cagaagagaa	aggatcatgt	+2350
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	+2651	tatcaatgga	tctgttccct	ggagataaat	ccccaaagtg	aaattactta	+2700
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	+2751	atcaaccagt	gcaaacaaatc	cccccatcaa	tacacagtag	tgccctgccc	+2800
	+2801	tctccccccg	aggtcttccg	aggcccttcc	tccgtgcctg	aacccctcgg	+2850
	+2851	acatatcata	tggcaaaactg	aagtgtccaa	cgagatatag	gaagtgaaac	+2900
	+2901	acgatgtaca	ctgaaacctg	caatacaaat	atgcagcatg	aagtgcctcg	+2950
	+2951	gttcactaac	ccgagctacg	ctgggtgcctt	cttttctacc	acttttctta	+3000

Year	Country	Population (millions)	Urban population (millions)	Urban population (%)
1980	China	959	190	19.8
1985	China	1059	220	20.8
1990	China	1159	250	21.6
1995	China	1259	280	22.3
2000	China	1359	310	22.8
2005	China	1459	340	23.3
2010	China	1559	370	23.8
2015	China	1659	400	24.1
2020	China	1759	430	24.5
2025	China	1859	460	24.8
2030	China	1959	490	25.0
2035	China	2059	520	25.3
2040	China	2159	550	25.5
2045	China	2259	580	25.7
2050	China	2359	610	25.9
2055	China	2459	640	26.1
2060	China	2559	670	26.3
2065	China	2659	700	26.5
2070	China	2759	730	26.6
2075	China	2859	760	26.7
2080	China	2959	790	26.8
2085	China	3059	820	26.9
2090	China	3159	850	27.0
2095	China	3259	880	27.1
2100	China	3359	910	27.2
2020	India	1029	210	20.4
2025	India	1129	240	21.3
2030	India	1229	270	22.0
2035	India	1329	300	22.6
2040	India	1429	330	23.1
2045	India	1529	360	23.5
2050	India	1629	390	24.0
2055	India	1729	420	24.4
2060	India	1829	450	24.7
2065	India	1929	480	25.0
2070	India	2029	510	25.3
2075	India	2129	540	25.5
2080	India	2229	570	25.7
2085	India	2329	600	26.0
2090	India	2429	630	26.2
2095	India	2529	660	26.4
2100	India	2629	690	26.5
2020	USA	279	190	68.1
2025	USA	289	195	67.5
2030	USA	299	200	66.9
2035	USA	309	205	66.4
2040	USA	319	210	65.9
2045	USA	329	215	65.4
2050	USA	339	220	65.0
2055	USA	349	225	64.5
2060	USA	359	230	64.1
2065	USA	369	235	63.7
2070	USA	379	240	63.3
2075	USA	389	245	63.0
2080	USA	399	250	62.7
2085	USA	409	255	62.4
2090	USA	419	260	62.1
2095	USA	429	265	61.8
2100	USA	439	270	61.5

Figure 6

Growth hormone 1
 5 Gene symbol : *GHI*
 Location : 17q

1 2
 -26 ATG GCT ACA G↓GC TCC CGG ACG TCC CTG CTC CTG GCT TTT GGC CTG -12
 Met Ala Thr G ly Ser Arg Thr Ser Leu Leu Leu Ala Phe Gly Leu

10 -11 CTC TGC CTG CCC TGG CTT CAA GAG GGC AGT GCC TTC CCA ACC ATT 4
 Leu Cys Leu Pro Trp Leu Gln Glu Gly Ser Ala Phe Pro Thr Ile

15 5 CCC TTA TCC AGG CTT TTT GAC AAC GCT AGT CTC CGC GCC CAT CGT 19
 Pro Leu Ser Arg Leu Phe Asp Asn Ala Ser Leu Arg Ala His Arg

20 2 3
 20 CTG CAC CAG CTG GCC TTT GAC ACC TAC CAG GAG TTT↓GAA GAA GCC 34
 Leu His Gln Leu Ala Phe Asp Thr Tyr Gln Glu Phe Glu Glu Ala

20 35 TAT ATC CCA AAG GAA CAG AAG TAT TCA TTC CTG CAG AAC CCC CAG 49
 Tyr Ile Pro Lys Glu Gln Lys Tyr Ser Phe Leu Gln Asn Pro Gln

25 50 ACC TCC CTC TGT TTC TCA GAG TCT ATT CCG ACA CCC TCC AAC AGG 64
 Thr Ser Leu Cys Phe Ser Glu Ser Ile Pro Thr Pro Ser Asn Arg

30 3 4
 65 GAG GAA ACA CAA CAG AAA TCC↓AAC CTA GAG CTG CTC CGC ATC TCC 79
 Glu Glu Thr Gln Gln Lys Ser Asn Leu Glu Leu Leu Arg Ile Ser

80 CTG CTG CTC ATC CAG TCG TGG CTG GAG CCC GTG CAG TTC CTC AGG 94
 Leu Leu Leu Ile Gln Ser Trp Leu Glu Pro Val Gln Phe Leu Arg

95 AGT GTC TTC GCC AAC AGC CTG GTG TAC GGC GCC TCT GAC AGC AAC 109
 Ser Val Phe Ala Asn Ser Leu Val Tyr Gly Ala Ser Asp Ser Asn

35 110 GTC TAT GAC CTC CTA AAG GAC CTA GAG GAA GGC ATC CAA ACG CTG 124
 Val Tyr Asp Leu Leu Lys Asp Leu Glu Glu Gly Ile Gln Thr Leu

4 5
 125 ATG GGG↓AGG CTG GAA GAT GGC AGC CCC CGG ACT GGG CAG ATC TTC 139
 Met Gly Arg Leu Glu Asp Gly Ser Pro Arg Thr Gly Gln Ile Phe

40 140 AAG CAG ACC TAC AGC AAG TTC GAC ACA AAC TCA CAC AAC GAT GAC 154
 Lys Gln Thr Tyr Ser Lys Phe Asp Thr Asn Ser His Asn Asp Asp

155 GCA CTA CTC AAG AAC TAC GGG CTG CTC TAC TGC TTC AGG AAG GAC 169
 Ala Leu Leu Lys Asn Tyr Gly Leu Leu Tyr Cys Phe Arg Lys Asp

45 170 ATG GAC AAG GTC GAG ACA TTC CTG CGC ATC GTG CAG TGC CGC TCT 184
 Met Asp Lys Val Glu Thr Phe Leu Arg Ile Val Gln Cys Arg Ser—

50 185 GTG GAG GGC AGC TGT GGC TTC TAG
 Val Glu Gly Ser Cys Gly Phe *

Figure 7

GH variant *Glu-Gly30*
 5 Location : 17q

1 2
 -26 ATG GCT ACA G↓GC TCC CGG ACG TCC CTG CTC CTG GCT TTT GGC CTG -12
 Met Ala Thr G ly Ser Arg Thr Ser Leu Leu Leu Ala Phe Gly Leu

10 -11 CTC TGC CTG CCC TGG CTT CAA GAG GGC AGT GCC TTC CCA ACC ATT 4
 Leu Cys Leu Pro Trp Leu Gln Glu Gly Ser Ala Phe Pro Thr Ile

5 CCC TTA TCC AGG CTT TTT GAC AAC GCT AGT CTC CGC GCC CAT CGT 19
 Pro Leu Ser Arg Leu Phe Asp Asn Ala Ser Leu Arg Ala His Arg

15 20 CTG CAC CAG CTG GCC TTT GAC ACC TAC CAG GAG TTT↓GGG GAA GCC 34
 Leu His Gln Leu Ala Phe Asp Thr Tyr Gln Glu Phe Gly Glu Ala

35 TAT ATC CCA AAG GAA CAG AAG TAT TCA TTC CTG CAG AAC CCC CAG 49
 Tyr Ile Pro Lys Glu Gln Lys Tyr Ser Phe Leu Gln Asn Pro Gln

20 50 ACC TCC CTC TGT TTC TCA GAG TCT ATT CCG ACA CCC TCC AAC AGG 64
 Thr Ser Leu Cys Phe Ser Glu Ser Ile Pro Thr Pro Ser Asn Arg

25 65 GAG GAA ACA CAA CAG AAA TCC↓AAC CTA GAG CTG CTC CGC ATC TCC 79
 Glu Glu Thr Gln Gln Lys Ser Asn Leu Glu Leu Leu Arg Ile Ser

80 CTG CTG CTC ATC CAG TCG TGG CTG GAG CCC GTG CAG TTC CTC AGG 94
 Leu Leu Leu Ile Gln Ser Trp Leu Glu Pro Val Gln Phe Leu Arg

30 95 AGT GTC TTC GCC AAC AGC CTG GTG TAC GGC GCC TCT GAC AGC AAC 109
 Ser Val Phe Ala Asn Ser Leu Val Tyr Gly Ala Ser Asp Ser Asn

35 110 GTC TAT GAC CTC CTA AAG GAC CTA GAG GAA GGC ATC CAA ACG CTG 124
 Val Tyr Asp Leu Leu Lys Asp Leu Glu Glu Gly Ile Gln Thr Leu

4 5
 125 ATG GGG↓AGG CTG GAA GAT GGC AGC CCC CGG ACT GGG CAG ATC TTC 139
 Met Gly Arg Leu Glu Asp Gly Ser Pro Arg Thr Gly Gln Ile Phe

40 140 AAG CAG ACC TAC AGC AAG TTC GAC ACA AAC TCA CAC AAC GAT GAC 154
 Lys Gln Thr Tyr Ser Lys Phe Asp Thr Asn Ser His Asn Asp Asp

155 GCA CTA CTC AAG AAC TAC GGG CTG CTC TAC TGC TTC AGG AAG GAC 169
 Ala Leu Leu Lys Asn Tyr Gly Leu Leu Tyr Cys Phe Arg Lys Asp

45 170 ATG GAC AAG GTC GAG ACA TTC CTG CGC ATC GTG CAG TGC CGC TCT 184
 Met Asp Lys Val Glu Thr Phe Leu Arg Ile Val Gln Cys Arg Ser

185 GTG GAG GGC AGC TGT GGC TTC TAG
 50 Val Glu Gly Ser Cys Gly Phe *

Figure 8

WT-HIS vs VAR 14

